Switching to X-Ray or E-Beam for sterilization of medical devices

View from a Notified Body

Günther Burgstaller

TÜV Süd PS GmbH

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Add value.
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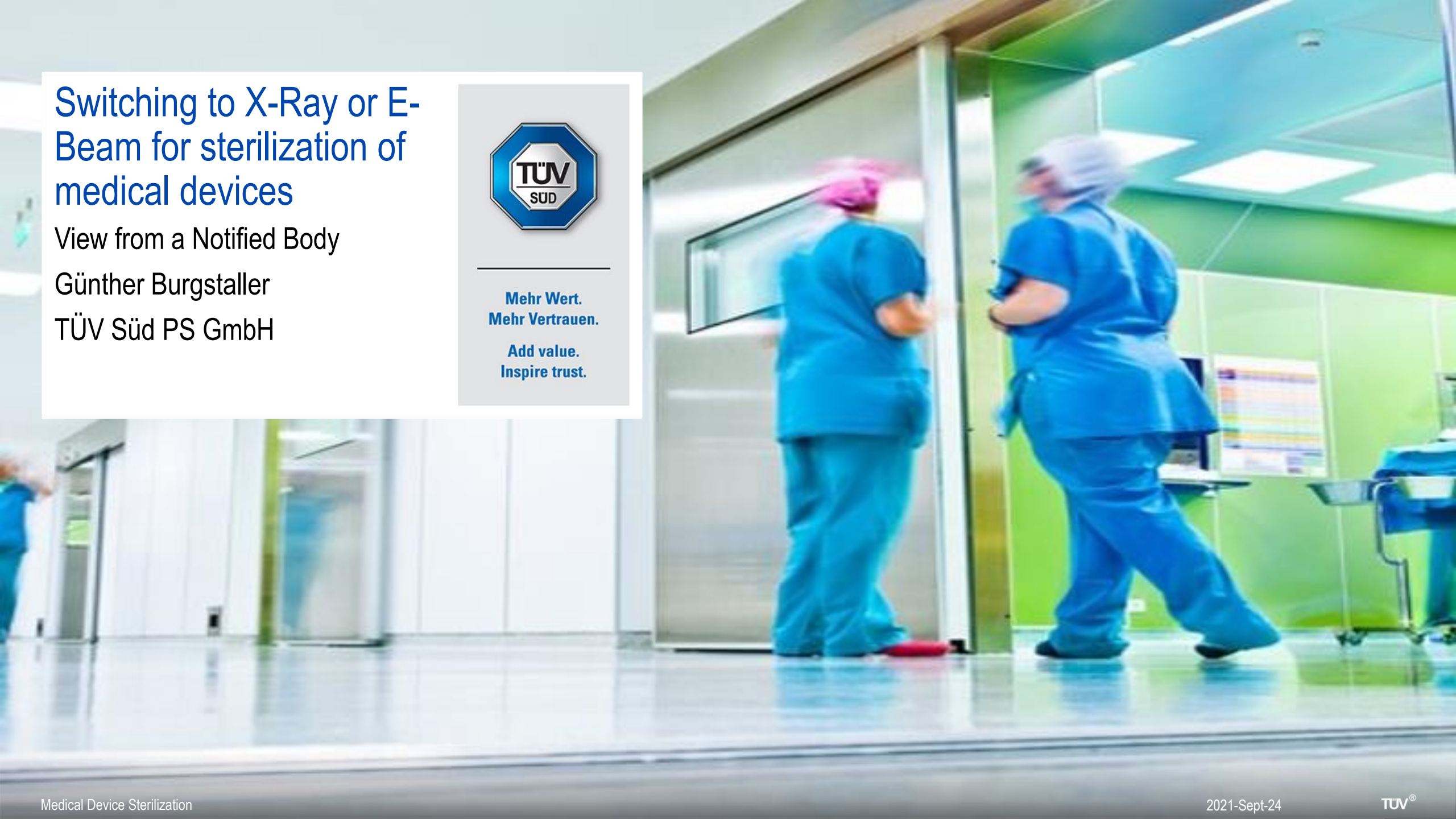

Topics

- Notified bodies
- Regulations and transition periods
- State of the art
- Standards
- Documentation for change notification
- Deficiencies

Disclaimer

General

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This does not preclude general training activities that are not client specific and that relate to regulation of devices or to related standards as well as technical meetings for the purpose of exchange of technical information and regulatory guidance between TÜV SÜD Product Service GmbH and a manufacturer applying for conformity assessment.
Please refer to the test and certification regulations of TÜV SÜD for further information:

http://www.tuvsud.com/ps-gtc

Regulatory approval in the EU

Notified Bodies (NB)

Nando:

https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.main

- 23 NB‘s for MDR

Bodies Found : 23

Search criteria :

Legislation : Regulation (EU) 2017/745 on medical devices
Procedure / Article or annex : ALL
Products : ALL
Horizontal technical competence : ALL

Search

Withdrawn/Expired/Suspended Notifications/NBs are not displayed in this list, you can find them in the Body module under the hyperlink "Withdrawn/Expired/Suspended Notifications/NBs"

Body type	Name	Country
NB 2265	3EC International a.s.	Slovakia
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary
NB 1912	DARE!! Services B.V.	Netherlands
NB 0344	DEKRA Certification B.V.	Netherlands
NB 0124	DEKRA Certification GmbH	Germany
NB 2460	DNV Product Assurance AS	Norway
NB 0297	DQS Medizinprodukte GmbH	Germany
NB 0537	Eurofins Expert Services Oy	Finland
NB 0477	Eurofins Product Testing Italy S.r.l.	Italy
NB 0459	GMED SAS	France
NB 0051	IMQ ISTITUTO ITALIANO DEL MARCHIO DI QUALITÀ S.P.A.	Italy
NB 0373	ISTITUTO SUPERIORE DI SANITA'	Italy
NB 2862	Intertek Medical Notified Body AB	Sweden
NB 0476	KIWA CERMET ITALIA S.P.A.	Italy
NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany
NB 0482	MEDCERT ZERTIFIZIERUNGS- UND PRÜFUNGSGESELLSCHAFT FÜR DIE MEDIZIN GMBH	Germany
NB 0050	National Standards Authority of Ireland (NSAI)	Ireland
NB 0598 (ex-0403)	SGS FIMKO OY	Finland
NB 1936	TUV Rheinland Italia SRL	Italy
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH Zertifizierstellen	Germany
NB 2696	UDEM Adriatic d.o.o.	Croatia

Simplified interaction of involved parties

Com = Commission

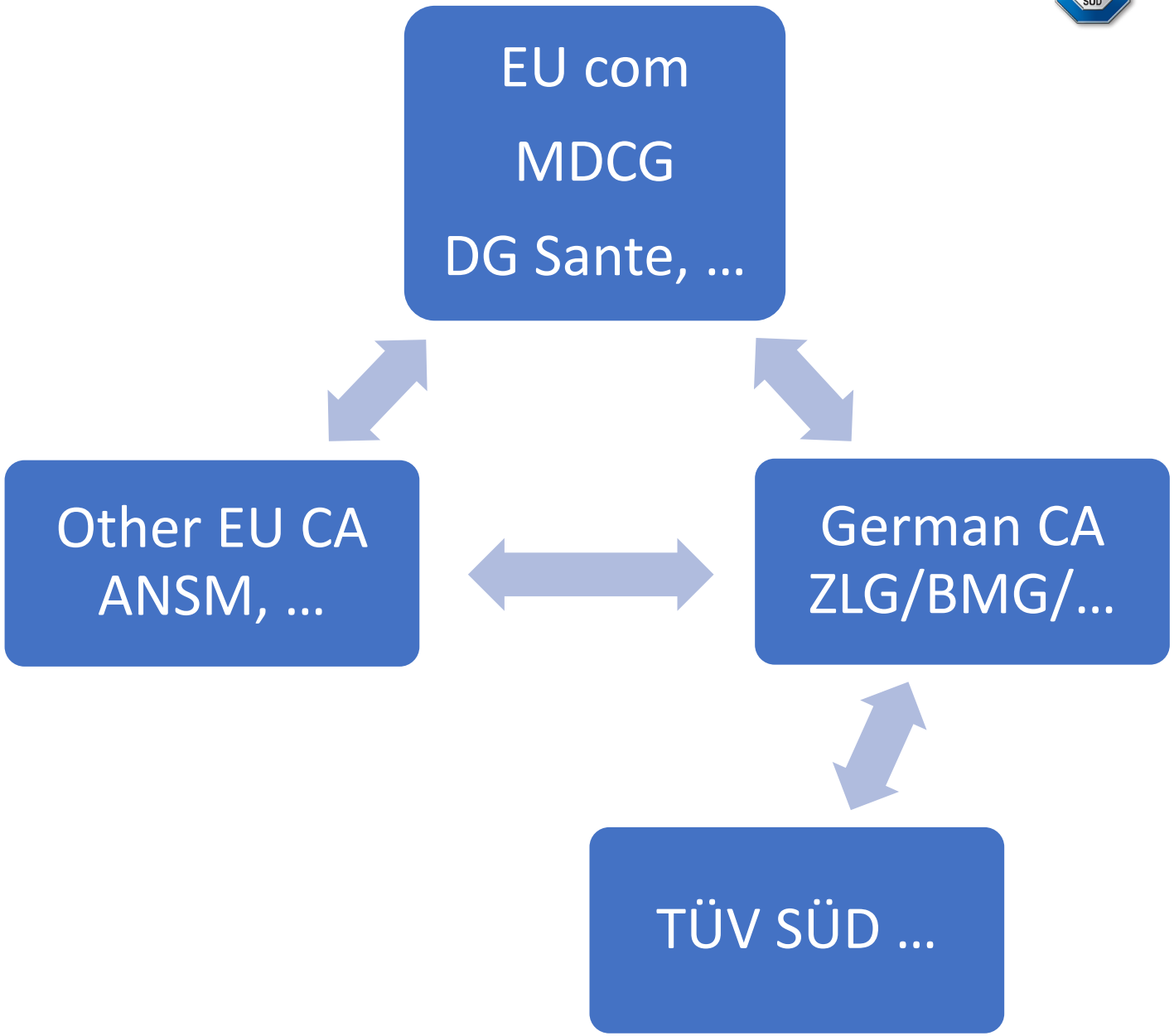
MDCG = Medical Device coordination Group

DG SANTE = Directorate-General for Health and Food Safety

BMG = German Ministry of Health

CA = Competent Authority

NB = Notified Body



MDR Annex I – GSPR

https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=DE

Requirement 1

- …..they shall be safe and effective and shall not compromise the clinical condition or the safety of patients,
- …. taking into account the generally acknowledged state of the art.
- The manufacturer shall establish, implement, document and maintain a risk management system.
- Risk management is a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic update.

State of the art - MDCG 2021-5

https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2021_5_en.pdf

is not a legally defined concept - involves several and complex aspects - difficult to be expressed in a single and clear definition.

Examples:

- "*The concept of essential requirements is* ***based on the assumption that the harmonised standards reflect generally acknowledgeable state of the art*** *and the ESO review standards regularly*" ("The 'Blue Guide' on the implementation of EU product rules"39, section 4.1.2.5., p. 49).
- "*The* ***most recent editions of standards*** *published by the standardisers should be considered as reflecting state-of-the-art, regardless of the OJ referencing*" (COM statement, Minutes of the meeting of the MDCG Subgroup on Standards held on 20 May 2019 40, item 3, p. 1).
- "*State of the Art:* ***Developed stage of technical capability at a given time as regards products, processes and services, based on the relevant consolidated findings of science, technology and experience.*** *NOTE 1: The state of the art embodies what is currently and* ***generally accepted as good practice*** *in technology and medicine. The state of the art does n****ot necessarily imply the most technologically advanced solution****. The state of the art described here is sometimes referred to as the 'generally acknowledged state of the art'. (Modified from ISO/IEC Guide 2:2004)*" (IMDRF/GRRP WG/N47 FINAL:2018 Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices 42, 3.43, p. 11).

State of the art / some Standards

ISO 13485:2016/AC:2018 Documentation / Validation of Process

EN ISO 14937:2009 Validation and characterization of sterilization processes in general

EN 556-1 Defines „sterile“ level (SAL) for products labeled “sterile”

EN ISO 11137-1:2015/A2:2019 Development, validation and routine control

EN ISO 11137-2:2015 Establishing the sterilization dose

EN ISO 11137-3:2017 Dosimetry aspects

ISO/TS 11137-4:2020 Process control

ISO TS 13004: VDmaxSD

EN ISO 11737-1:2018 Determination of bioburden

EN ISO 11737-2:2020 Test of sterility

AAMI ST72 Pyrogens

AAMI TIR 29:2017 Guide for process characterization and control (superseded by ISO/TS 11137-4)

AAMI TIR 35:2016 Alternative Sampling plans / Product adoption

AAMI TIR 17:2017 Material qualification

AAMI ST67 Requirements and guidance for selecting a sterility assurance

ISO ASTM 51261 calibration routine dosimeters

ISO ASTM 51275 radiochromic film dosimeters

ISO ASTM 51276 PMMA Dosimeters

ISO ASTM 51607 Alanine Dosimeters

ISO ASTM 51608 dosimetry x-ray

ISO ASTM 51631 calorimetric dosimetry e-beam

ISO ASTM 51649 dosimetry e-beam

ISO ASTM 51702 dosimetry gamma

ISO ASTM 51707 estimation of uncertainty

ISO ASTM 52303 Dose Mapping

ISO ASTM 52628 Dosimetry

ISO ASTM 52701 performance charachteristics of dosimeters

Standards are ‚voluntary‘

- ....choosing to use a standard or not, as appropriate and applicable, belongs to the manufacturer, within its overall and ultimate responsibility on the legal compliance of products intended to be placed on the EU market. (MDCG 2021-05)
- ... provide a level of protection that is equivalent to that provided by harmonised standards;
- Deviating approaches to ISO 11137 are acceptable if appropriately justified (e.g. ISO TS 13004, AAMI TIR 35)

ISO 11137-1: 8.4 Transference of VD, D_{ster} and $D_{max,acc}$

$D_{max,acc}$

- Assessment if differences in operating conditions (e.g. dose rate, temperature) do not affect product performance
- Higher dose rate → unwanted effects upon product are less likely

VD, D_{ster}

Show that differences in operating conditions of the two radiation sources have no effect on microbicidal effectiveness

- Transference of VD and D_{ster} is always allowed from gamma to different gamma facility

For E-Beam and X-Ray:

- For dry products:, transference of VD and D_{ster} is allowed between identical technology (e.g. from E-beam to E-beam)
- For products which contain water the radiation sources have to operate under identical conditions.

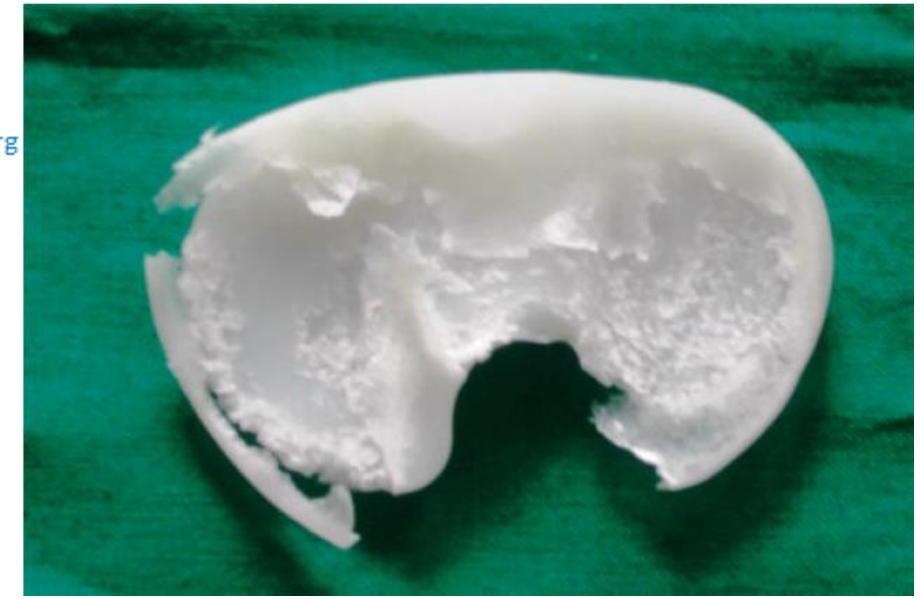
Risk based approach

- microbial growth promoting devices (moisture)
- devices with critical long-term mechanical performance (e.g. knee implants)
- interaction of product and packaging
- devices where biocompatibility might change

Journal of the Mechanical Behavior of Biomedical Materials
Volume 122, October 2021, 104652

Influence of radiation conditions on the wear behaviour of Vitamin E treated UHMWPE gliding components for total knee arthroplasty after extended artificial aging and simulated daily patient activities

Jens Schwiesau [a, c], Bernhard Fritz [a], Georg
Thomas M. Grupp [a, c]



Destroyed Tibiainlay, Utzschneider S, Paulus AC, Schröder C, Jansson V. Possibilities and limits of modern polyethylenes. With respect to the application profile. Orthopade. 2014 Jun;43(6):515-21

EO as previous technology

clause 8.4 does not apply

-> full spectrum of validation necessary

+ packaging validation according to ISO 11607

Undesirable effects Mitigation measures

- Cooling
  - e.g. by dry ice

  Note: alters the response of dosimeters
  -> in dose mapping use surrogate material
- Vacuum packaging in inert gas atmosphere (minimize oxidization)
- For both: modification of kill effect needs to be considered in microbiological validation

Wikimedia Commons contributors, "File:Dry Ice 3.jpg," Wikimedia Commons, the free media repository.

Wikimedia Commons contributors, "File:Vacuum packaged meat raw.jpg," *Wikimedia Commons, the free media repository*

Old versus new EU regulation

MDR §120(3): changes during transition period

(…) A device with a certificate that was issued in accordance with Directive (…) may only be placed on the market or put into service (…) provided there are no significant changes in the design and intended purpose.

- Article 120 is applicable to **all** devices with a certificate independent of conformity assessment procedure and class (Ix, IIa; IIb, III).

➔Changes not related to design and intended purpose are allowed.

Guidance is provided in MDCG 2020-03

https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_guidance_significant_changes_annexes_en.pdf

Significant ≠ Significant (change)

- Significant in **MDR §120** (guidance in MDCG 2020-03) means switch to MDR before significant change is implemented
- changing sterilization technology is a significant **NBOG-BPG 2014-3** change for which a change notification (CN) has to be submitted to your NB
- Switching from Gamma to X-Ray or E-Beam is not considered significant (MDR §120) but significant related to (NBOG-BPG 2014-3)
- Switching from Ethylene oxide to Radiation sterilization is considered significant (MDR §120)

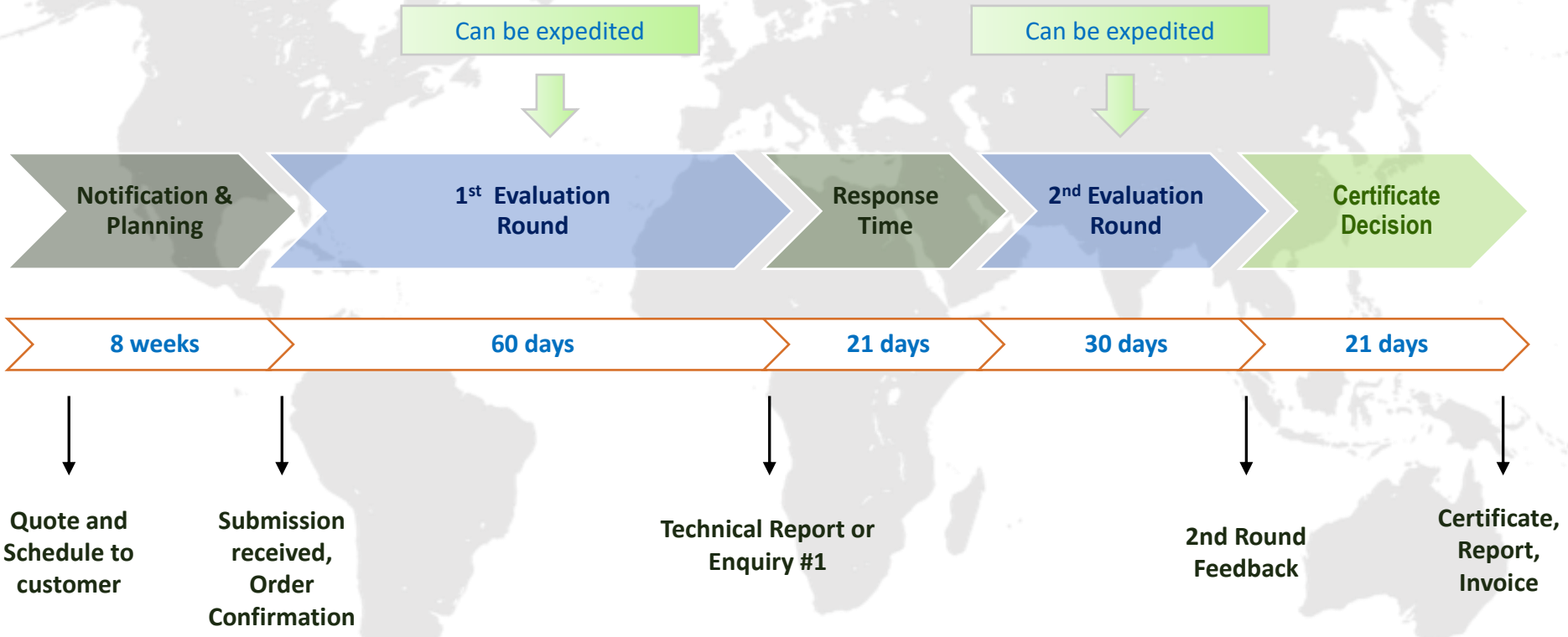
Summary

when you decided to change your sterilization technology

- after performing the feasibility studies
- and taking into account the state of the art
- and before implementation of the change
- check with **your** notified body about procedures and timelines, forms and checklists

TÜV SÜD Technical Documentation Service Model

Standard Timeline – 90 workdays + 8 weeks prenotification



TÜV SÜD Forms and checklists

https://www.tuvsud.com/en/industries/healthcare-and-medical-devices/medical-devices-and-ivd/questionnaires-and-application-forms-for-medical-devices

Appendix D

Plans for substantial change(s) to the quality management system/product

Manufacturer:

Application identification:

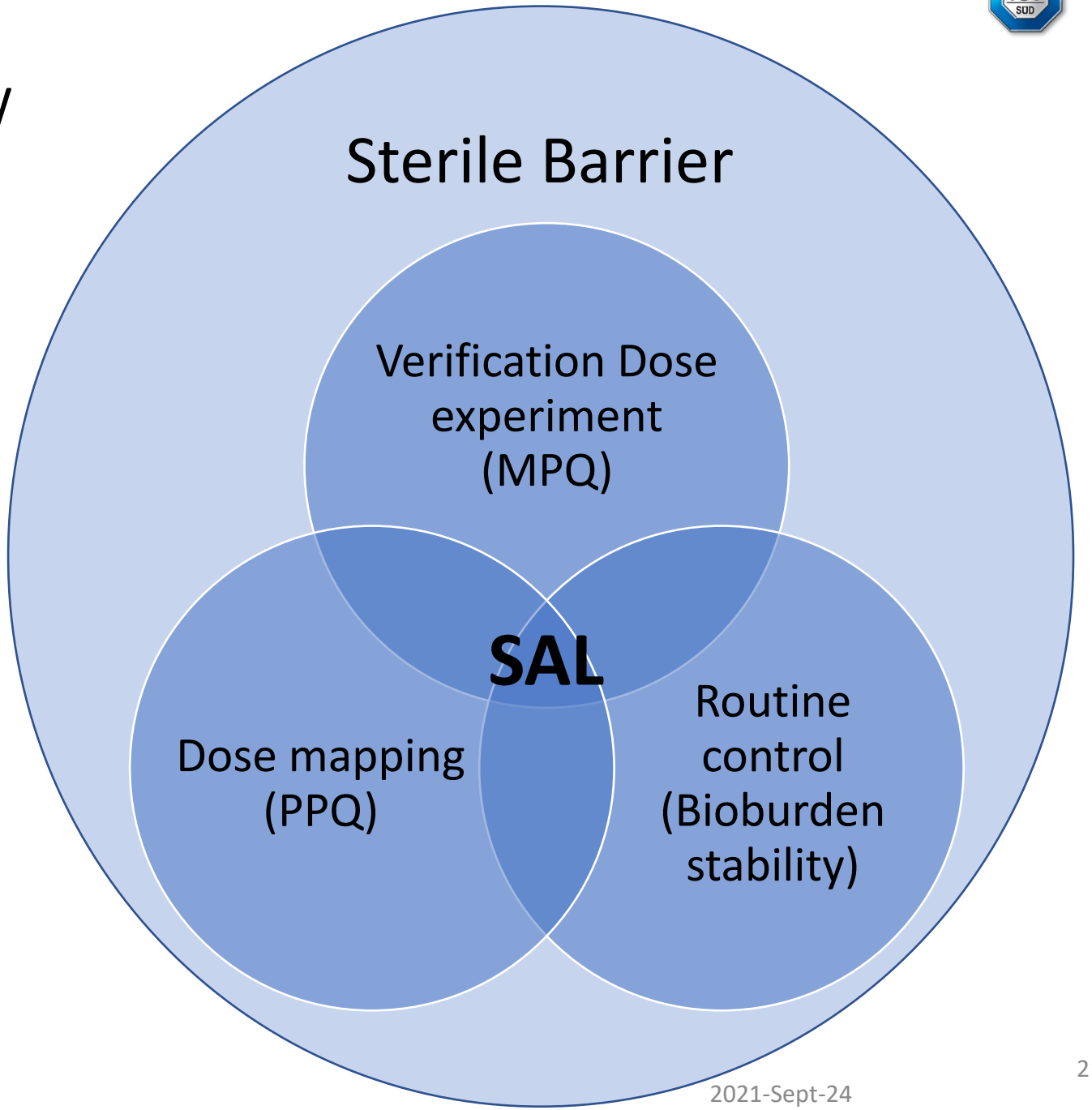
https://www.tuvsud.com/en/industries/healthcare-and-medical-devices/sterilisation-practices-control-and-validation/biological-safety-checklists

Client Checklist Irradiation Sterilization

Notified Body (NB) review

Evidence/discussion/justification that product performance after change fulfills specification and regulations:

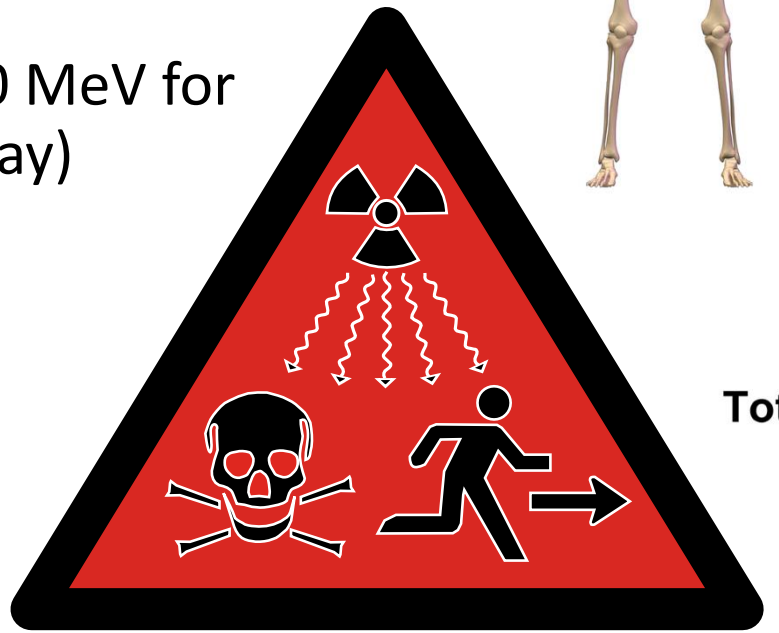
1. Sterility Assurance (SAL)
2. Packaging Performance (sterility is maintained during transport and shelf life after irradiation with worst case dose)

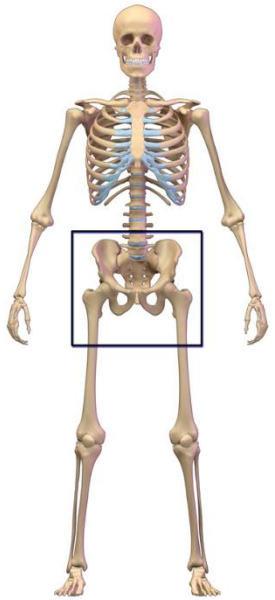


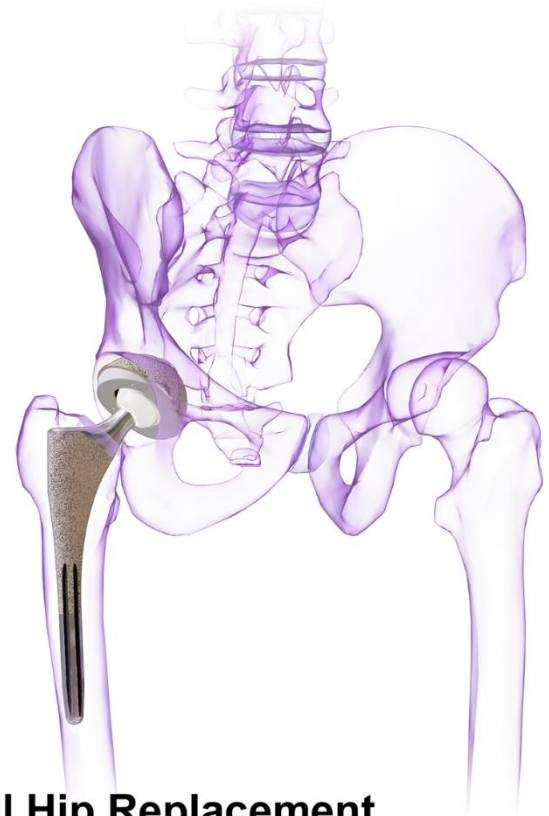
Notified Body (NB) review

Check performance after irradiation with worst case dose and throughout lifetime of device:

3. Biocompatibility
4. Product functionality
5. Induced radioactivity (E > 10 MeV for E-beam or E > 5 MeV for X-ray)







Total Hip Replacement

Documentation to be submitted for CN

- Change Notification form / Updated list of critical suppliers
- Quality Management and/or accreditation **certificates of suppliers (including attachments)**
- Validation **plan(s)** & report(s)
- Dose Audit and Bioburden **History**
- Bioburden and Sterility **Test Method validation**
- Identification and description of used sterilization equipment and **conveyor system**
- Description of the **load and how it is exposed to radiation** (orientation, density, packaging) and **why it is representative** for the routine sterilization load.
- List of **all affected products**

Deficiencies and issues that delay assessment

- Read suppliers test reports **before** submitting them to the NB (Is the report conclusive? Did all tests pass? Are there deviations which need clarification?)
- Describe what was done, when, how, under which circumstances
- Involve **competent persons** (Microbiology, Physics, etc.)
- Make your **pdf's searchable** (OCR) and allow comments and highlighting in document
- Justify if standard or guidance is not followed
- Traceability: is it clear for each report if it is applicable for the product?
- Provide structure and table of contents to submission package
- Get in touch with the assessor / clarify misunderstandings

Physical PQ - Dose mapping

Check regions with suspicion of:

- shielding effects
- dose accumulation (E-Beam)
- transitions of densities

At least three **reproducible** runs.

- For each deviating load (min/max)
- sufficient number of dosimeters in every run
- Justify if some zones are not dose mapped

Physical PQ - Dose mapping

E-Beam dose mapping is more complicated:

- usually, dosimeters have to be placed inside packaging (critical evaluation/simulation before actual dosemapping)
- Natural variation of dose due to varying (e.g. moving) load + dosimetry uncertainty can sum up to total budget of 10% or more. Both shall be considered.
- Good examples for different technologies in ISO/TS 11137-4

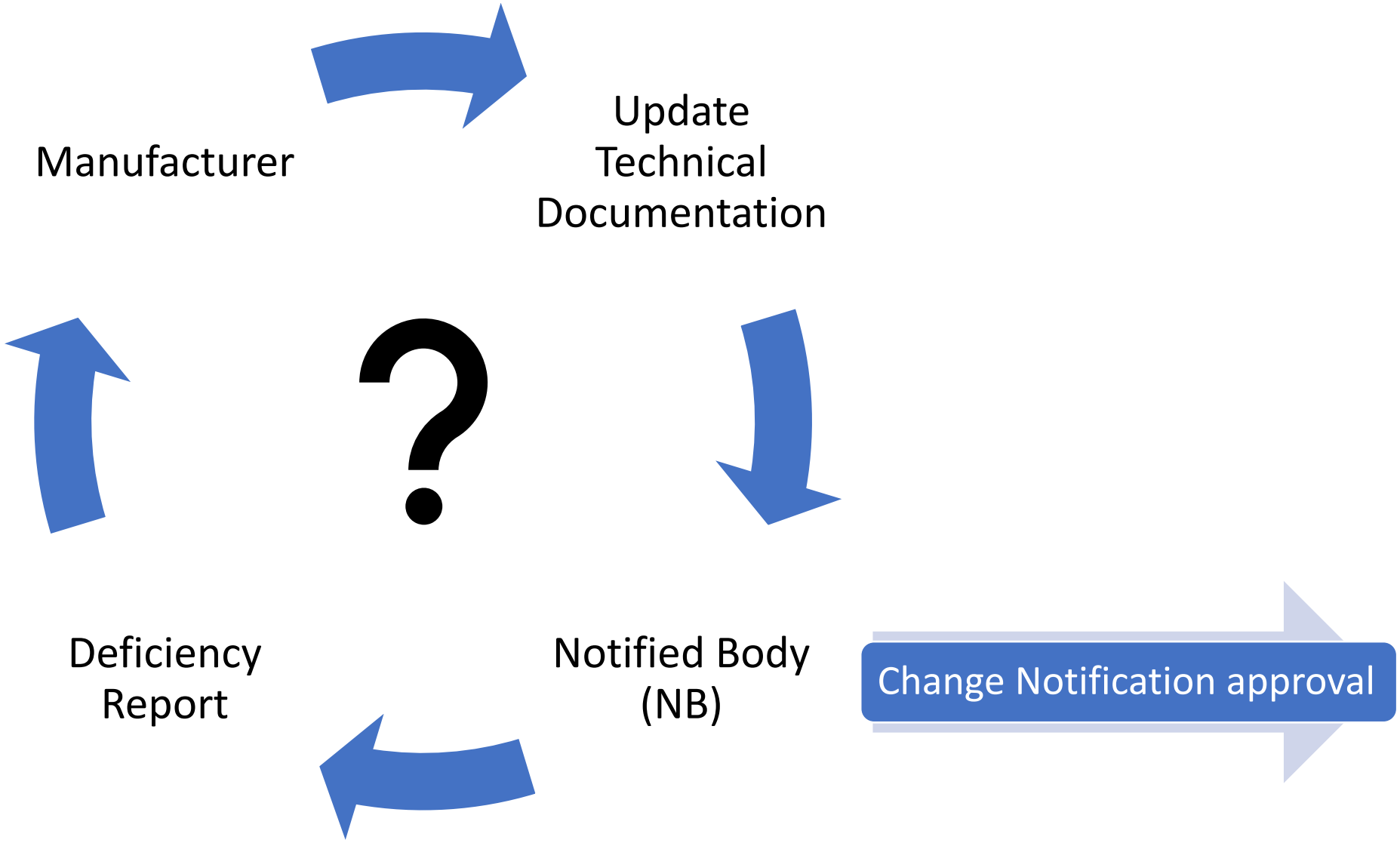
Microbiological PQ - Verification Dose experiment

- Did changes (also improvements) **accumulate** which justify an adaption of the verification dose
- Do all members product families have bioburden similar in numbers **and types**?
- Do not use limit of detection (e.g. „Bioburden < 10 CFU -> 10 CFU should not be used for Verification Dose determination)
- Provide test or rationale if anaerobic microorganisms are not considered.
- Adjust bioburden action limit to bioburden history (e.g. no general 1000 CFU for VDmax25)

Summarize and document results and conclusions

- dose range at routine monitoring position(s)
- load variations (e.g. density, product variants)
- bioburden variation (single/average)

Regulatory approval in the EU



What next?

- Read regulations, standards, guidances and scientific literature (not just abstract and summary)
- Switch to E-Beam or X-Ray
- Share your data and experience